UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,980	04/07/2005	Andrea Amalfitano	180/151 PCT/US	7130

25297 7590 02/22/2008

JENKINS, WILSON, TAYLOR & HUNT, P. A.
3100 TOWER BLVD., Suite 1200
DURHAM, NC 27707

EXAMINER	
SAJJADI, FEREYDOUN GHOTB	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
02/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,980	AMALFITANO ET AL.	
	Examiner	Art Unit	
	FEREYDOUN G. SAJJADI	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-142* is/are pending in the application.

4a) Of the above claim(s) *8,16,24,25,29,34 and 37-142* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9-15,17-23,26-28,30-33,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/15/2004 & 4/25/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Status

This action is in response to papers filed December 3, 2007. Applicant's response to restriction requirement of October, 2007 has been entered. No claims were cancelled, amended or newly added. Currently, claims 1-142 are pending in the application, and claims 37-142 stand withdrawn from consideration, without traverse, pursuant to the office action dated January 17, 2007. Claims 1-36 were subject to a species restriction requirement in the previous office action dated October 2, 2007.

Response to Election/Restrictions

Applicants' election of the species of AAV2 inverted terminal repeats, AAV p5 promoter operably linked to AAV Rep, E4orf6 functional genomic region, deleted preterminal and polymerase regions, liver-specific promoter operably linked to a heterologous nucleic acid, and acid glucosidase (GAA) as the therapeutic heterologous polypeptide, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In view of teachings of the prior art of record, and upon further consideration, the restriction between the species of reporter polypeptide and therapeutic polypeptide is hereby withdrawn. As the restriction is still deemed proper, the requirement for restriction is maintained and hereby made FINAL. The instant claims have been examined commensurate with the scope of the elected species. Accordingly, claims 8, 16, 24, 25, 29 and 34 have been additionally withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected subject matter, there being no allowable generic or linking claim.

Applicant timely responded to the restriction (election) requirement in the reply filed December 3, 2007. Claims 1-7, 9-15, 17-23, 26-28, 30-33, 35 and 36 are under current examination.

Information Disclosure Statement

The information disclosure statements filed 11/15/2004 and 4/25/2005 have been considered and indicated as such on Forms PTO-1449.

Objections to the Specification/Abstract

Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. In the instant case, the abstract employs legal phraseology. Appropriate correction is required.

Objections to the Oath/Declaration

This Application is a 371 national stage entry of PCT/US03/13323, claiming priority to U.S. Provisional Application No. 60/376,397, filed April 30, 2002. The provisional Application has been indicated as a foreign Application and benefit of priority claimed under 35 USC § 119(a)-(d), or (f) of 365(a) or (b). However, the U.S. Provisional Application is not a foreign Application, and such claim should be made under 35 USC § 119(e). Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 12, 15, 17-22, 26, 27, 35 and 36 are rejected under 35 U.S.C. 102(b) as being anticipated by Lieber et al. (J. Virol. 73(11):9314-9324; 1999, of record).

The claims embrace a recombinant adenovirus/AAV hybrid virus comprising an adenovirus vector genome deleted in the polymerase region, or the preterminal protein region, or both; comprising AAV2 inverted terminal repeats (ITRs) and cis-elements for viral replication, packaging and encapsidation, further comprising a heterologous nucleic acid sequence, and wherein the hybrid virus does not encode the AAV rep or AAV capsid proteins.

Lieber et al. teach integrating adenovirus-AAV hybrid vectors devoid of all viral genes (Title). Further teaching that ITRs inserted into adenovirus (Ad) vector genomes resulting in vector genomes devoid of all viral genes, are efficiently packaged into functional Ad capsids (Abstract). The Ad vectors contain AAV ITRs flanking a reporter gene cassette inserted into the E1 region; Ad.AAV vector genomes contain only the transgene flanked by AAV ITRs, and packaging signals (Abstract; the reporter transgene corresponding to a heterologous nucleic acid, limitation of claim 1(b)).

In Figure 1, Lieber et al. depict an Ad.AAV2 hybrid vector comprising a neo gene under the control of the SV40 and Tn5 promoters (limitation of claims 21, 22 and 27). As the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions (limitation of claim 1(a) (i-iii) and 17-20); and does not encode AAV Rep or AAV capsid proteins (limitation of claim 4), or E1 region products (limitation of claims 12 and 14). Lieber et al. additionally teach hybrid vectors containing the AAV2 genome ITRs (second column, p. 9315, Figure 1, and first column, first paragraph, p. 9317; limitation of claim 3).

With regard to the limitation of claim 15 for replication and production of hybrid virus in a helper cell, Lieber et al teach that viruses with different transgene cassettes incorporated into their E1 regions were generated by recombination of pXCJL1-derived shuttle plasmids and pJM17 (Microbix) in 293 cells; thus constituting a helper cell. Viruses containing two AAV ITRs tended to have deletions within the ITRs or other Ad sequences and to recombine with Ad sequences present within the 293 cell genome. Only plaques from viruses with intact ITRs were amplified, CsCl banded, and tittered (first column, p. 9315, under Adenoviruses; limitation of claims 15, 35 and 36).

Therefore by teaching all the limitations of the claims, Lieber et al. anticipate the instant invention as claimed.

Claims 1-3, 5-7, 9-13, 15, 17-22, 26, 27, 35 and 36 are rejected under 35 U.S.C. 102(e) as being anticipated by Mountz et al. (U.S. Patent No.: 6,383,794, filed Aug. 24, 1999), as evidenced by Samulski et al. (J. Virol. 63(9):3822-3828; 1989).

The claims embrace a recombinant adenovirus/AAV hybrid virus comprising an adenovirus vector genome deleted in the polymerase region, or the preterminal protein region, or both; comprising AAV2 inverted terminal repeats (ITRs) and cis-elements for viral replication, and encapsidation, further comprising a heterologous nucleic acid sequence, and wherein the vector genome encodes an AAV rep protein operably linked to the AAV p5 promoter.

Mountz et al. teach high titer recombinant AAV hybrid vectors encoding a therapeutic gene flanked by ITRs of AAV and the AAV rep and cap genes (Abstract and limitation of claims 1(b), 5, 9 and 27). In Example 1, Mountz et al. describe the construction of the hybrid Ad-AAV vector, by cloning the 4.2 kb Xba fragment fragment of AAV pSub201 containing the AAV rep and cap genes into the E1 Xba site of an adenoviral shuttle vector (column 13). The pSub201 is an infectious clone of AAV type 2 DNA (as evidenced by Samulski et al. second column, p. 3822; limitation of claim 3). The rep and cap genes are under the control of the AAV p5 promoter in the hybrid AdAAV vector, as shown in Fig. 1A (column 4; limitation of claims 6 and 7).

The recombinant AAV further comprises the adenoviral ITRs and an adenovirus packaging signal, El, E2A, E4 and VIA regions and no other adenoviral gene regions (see Fig. 15B, pages 42-44; limitation of claims 2). Mountz et al. state: "Preferably, the adenovirus genome is deleted for all coding sequences other than those genes required for adenoviral replication. More preferably, the genes required for adenoviral replication, and hence remaining on the adenoviral genome, are E1A, E1B, E2A, E4 and VIA." (column 7, last paragraph; limitation of claim 10). As the recombinant hybrid vector does not contain an E2B region, it necessarily is deficient in sequences encoding the preterminal and polymerase protein regions (limitation of claims 1(a) and 17-20). Further, the E4 region contains the E4orf6 (limitation of claim 11). The insertion of the genes required for replication is into an E1 deleted region of the vector (shown in Figs. 10 and 11; limitation of claims 12 and 13).

In Example 12, column 18, Mountz et al. state: "The helper-dependent recombinant adenoviruses, including AdrAAV8kb (FIG. 10B) and AdrAAV-GFP8kb (FIG. 10C) which produces high-titer, Ad-free rAAV, was constructed by deleting an 8 Kb PmeI-SgfI fragment encoding the Ad hexon, penton, core protein, and DNA polymerase genes from plasmid pAdAAV or pAdrAAV-GFP (FIG. 1A, FIG. 4A). This virus already has deletions in the E1 and E3 genes. Both constructs are able to replicate and be packaged in the presence of the Ad helper virus, AdLoxpTK, in 293CreNS cells." (limitation of claims 15, 35 and 36).

In Example 4, column 13, Mountz et al. describe the construction of a hybrid AdrAAV vector encoding a GFP protein operably linked to the CMV promoter (the GFP constituting a heterologous reporter polypeptide; limitation of claims 21 and 22, 26 and 27).

Therefore by teaching all the limitations of the claims, Mountz et al. anticipate the instant invention as claimed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 26-28 and 30-33 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lieber et al. (J. Virol. 73(11):9314-9324; 1999, of record), in view of Podsakoff et al. (U.S. Patent No.: 5,962,313; effective filed Jan. 16, 1997).

The claims encompass a recombinant adenovirus/AAV hybrid virus comprising an adenovirus vector genome deleted in the polymerase region, or the preterminal protein region, or both; comprising AAV2 inverted terminal repeats (ITRs) and cis-elements for viral replication, packaging and encapsidation, further comprising a heterologous nucleic acid sequence encoding human lysosomal acid α-glucosidase.

The instant specification identifies glycogen storage disease type II (GSD II) as a classical lysosomal storage disorder, mediated by Acid α-Glucosidase (second paragraph p. 2).

Lieber et al. describe integrating adenovirus-AAV hybrid vectors devoid of all viral genes (Title). Further teaching that ITRs inserted into adenovirus (Ad) vector genomes resulting in vector genomes devoid of all viral genes, are efficiently packaged into functional Ad capsids (Abstract). The Ad vectors contain AAV ITRs flanking a reporter gene cassette; Ad.AAV vector genomes contain only the transgene flanked by AAV ITRs, and packaging signals (Abstract; the reporter transgene corresponding to a heterologous nucleic acid, limitation of claim 1(b)).

In Figure 1, Lieber et al. depict an Ad.AAV2 hybrid vector comprising a neo gene under the control of the SV40 and Tn5 promoters (constituting a reporter polypeptide; limitation of claims 26 and 27). As the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions (limitation of claim 1(a) (i-iii)). Lieber et al. additionally teach hybrid vectors containing the AAV2 genome ITRs (second column, p. 9315, Figure 1, and first

column, first paragraph, p. 9317). The Ad.AAV vectors are described as a promising tool for stable gene transfer *in vitro* and *in vivo* (Abstract).

While Lieber et al. do not describe their hybrid AAV vector heterologous protein as human lysosomal acid α-glucosidase, the prior art had taught AAV vectors carrying a nucleic acid encoding for lysosomal acid α-glucosidase.

Podsakoff et al. describe AAV vectors comprising a gene encoding a lysosomal enzyme (Title). In Example 8 (column 27), Podsakoff et al. describe *in vitro* and *in vivo* transduction of muscle cells using a rAAV-hGAA vector encoding human lysosomal acid α-glucosidase to treat glycogen storage type II (Pompe's disease) (columns 27 and 28; limitation of claims 28 and 30-33).

The references of Lieber et al. and Podsakoff et al. are both directed to the use of recombinant AAV vectors for transfer of heterologous genes *in vitro* and *in vivo*. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to use the human lysosomal acid α-glucosidase of Podsakoff et al. in the hybrid AAV vector of Lieber et al. for gene transfer, with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to utilize the hybrid AAV vector of Lieber et al. for transfer of the human lysosomal acid α-glucosidase transgene for therapy, because such vectors could be produced at high titer and high purity (see Abstract, Lieber et al).

Claims 1 and 21-23 are rejected under 35 U.S.C. §103(a) as being unpatentable over Lieber et al. (J. Virol. 73(11):9314-9324; 1999, of record), in view of Souza et al. (U.S. Patent Application Publication No.: 2003/0017139; effective filed Nov. 16, 1999).

The claims encompass a recombinant adenovirus/AAV hybrid virus comprising an adenovirus vector genome deleted in the polymerase region, or the preterminal protein region, or both; comprising AAV2 inverted terminal repeats (ITRs) and cis-elements for viral replication, packaging and encapsidation, further comprising a heterologous nucleic acid sequence that is operatively associated with a liver-specific promoter.

Lieber et al. describe integrating adenovirus-AAV hybrid vectors devoid of all viral genes (Title). Further teaching that ITRs inserted into adenovirus (Ad) vector genomes resulting in vector genomes devoid of all viral genes, are efficiently packaged into functional Ad capsids (Abstract). The Ad vectors contain AAV ITRs flanking a reporter gene cassette; Ad.AAV vector genomes contain only the transgene flanked by AAV ITRs, and packaging signals (Abstract; the reporter transgene corresponding to a heterologous nucleic acid, limitation of claim 1(b)).

In Figure 1, Lieber et al. depict an Ad.AAV2 hybrid vector comprising a neo gene under the control of the SV40 and Tn5 promoters. As the hybrid vector genome does not include coding sequence for any adenoviral or AAV proteins, it necessarily comprises deletions of the adenovirus polymerase and preterminal protein regions (limitation of claim 1(a) (i-iii)). Lieber et al. additionally teach hybrid vectors containing the AAV2 genome ITRs (second column, p. 9315, Figure 1, and first column, first paragraph, p. 9317). The Ad.AAV vectors are described as a promising tool for stable gene transfer *in vitro* and *in vivo* (Abstract).

While Lieber et al. do not describe their hybrid AAV vector encoding a heterologous nucleic acid as operatively associated with a liver-specific promoter, such promoters were known in the prior art.

Souza et al. describe adeno-associated viral vectors comprising liver specific enhancer/promoter combinations linked to a transgene administered to recipient cells (Abstract). The references of Lieber et al. and Souza et al. are both directed to the use of recombinant AAV vectors for transfer of heterologous transgenes genes to recipient cells. Therefore, it would have been *prima facie* obvious for a person of ordinary skill in the art to use the liver-specific promoter of Souza et al. in the hybrid AAV vector of Lieber et al. for gene transfer, with a reasonable expectation of success, at the time of the instant invention. A person of skill in the art would be motivated to utilize the hybrid AAV vector of Lieber et al. for transfer of transgene operably linked to a liver-specific promoter for therapy, because such vectors could be produced at high titer and high purity (see Abstract, Lieber et al).

Conclusion

Claims 1-7, 9-15, 17-23, 26-28, 30-33, 35 and 36 are not allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FEREYDOUN G. SAJJADI whose telephone number is (571)272-3311. The examiner can normally be reached on 6:30 AM-3:30 PM EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Fereydoun G Sajjadi/
Examiner, Art Unit 1633